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Aging within the Stem Cell Niche

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Decreased adult stem cell function is thought to play a primary role in organismal aging. Two recent papers in *Cell Stem Cell* demonstrate the importance of signaling from the stem cell niche in the aging of *Drosophila* germline stem cells.

Despite being a process that virtually every eukaryotic organism undergoes, the cellular basis of aging has remained elusive. Because adult stem cells are responsible for maintaining tissue homeostasis throughout an organism's lifetime, an attractive theory is that aging-related phenotypes might be, at least in part, due to a decline in the number or function of tissue stem cells. A dramatic example in support of this theory is the recent demonstration that hair graying in mice is caused by a reduction in the number of melanocyte stem cells in the hair follicle (Nishimura et al., 2005). Similar declines in stem cell number and function have been observed in a variety of tissues and organisms (reviewed in Van Zant and Liang, 2003). An obvious next question is what causes this decline. Is it intrinsic to the stem cells or dependent on extrinsic factors? In either case, what specific molecular pathways might be involved in this decline?

A number of recent studies have demonstrated the importance of cell-extrinsic factors on aging of adult stem cells. For example, it has recently been shown that aged mouse spermatogonial stem cells can be serially transplanted into young recipient hosts for over 3 years without any decline in function, suggesting that the stem cells themselves may not change appreciably given a continuously young environment (Ryu et al., 2006). Similarly, satellite stem cells in muscle tissue from aged mice can continue to function without any decline in function when provided with systemic factors from a young mouse through parabiotic matings in which the mice have a shared circulatory system (Conboy et al., 2005). These satellite stem cell studies have further shown that in these cells, aging of the systemic environment results in altered Notch and Wnt signaling within stem cells, and age-related changes in stem cell function can be reproduced by altering these pathways directly (Brack et al., 2007). While these studies have moved us closer to understanding how an aging environment can affect stem cells, further investigations into the effects that aging has on the extrinsic environment has been limited in these systems by a lack of detailed understanding of the cells that contribute to form the stem cell niche, and the signals that these cells use to maintain stem cells.

In contrast to these systems, the stem cell niche for *Drosophila* germline stem cells (GSCs) has been well defined at the cellular and molecular levels. In both males and females, GSCs can be easily identified in vivo and are found tightly associated through adherens junctions to adjacent somatic niche cells that produce signals which act locally to maintain stem cell fate (reviewed in Fuller and Spradling, 2007). In the testis, the ligand unpaired is produced by these somatic cells to activate JAK/STAT signaling in the adjacent male GSCs, while in the ovary, somatic niche cells produce the ligands dpp and gbb, which activate the TGF-β pathway in adjacent female GSCs. Upon dividing, cells that move out of contact with these somatic cells and their signals go on to differentiate, while those within the niche retain stem cell fate. Previous work has demonstrated that in both the ovary and testis, GSCs are lost from the stem cell niche as flies age, although there appears to be a mechanism to replace stem cells to mitigate this loss over the lifespan of the organism (Wallenfang et al., 2006; Xie and Spradling, 2000). Additionally, studies in the male have shown that GSC division rate also decreases with age (Wallenfang et al., 2006). Two studies appearing in *Cell Stem Cell* have begun to identify how changes in the niche contribute to these changes in GSCs during aging (Boyle et al., 2007; Pan et al., 2007).

Though the paper by Boyle and colleagues focuses on aging of GSCs in the male while the article by Pan and colleagues examines GSCs in females, systems with distinct cellular architectures and signaling pathways, a number of common themes emerge. Both groups present evidence for a decline in signaling from niche cells that is used to maintain stem cells. In the testis, there is a decrease during aging in unpaired mRNA expression in niche cells, and in the ovary, expression of a lacZ reporter for TGF-β pathway activation significantly decreases during aging in GSCs. Further evidence that a decrease in signaling from the niche can lead to aging of GSCs comes from the observation that mutant flies heterozygous for gbb and dpp in the ovary show defects in GSC number and function at a younger age than wild-type flies. Both groups go on to show that by maintaining signaling at high levels, at least some of these aging-related declines can be minimized. In the testis, production of high levels of unpaired in the niche leads to a maintenance of GSC number, though proliferation of GSCs continues to decline with age. Similarly, in the ovary, high levels of gbb production in the niche also leads to GSC maintenance (interestingly, high levels of dpp, the other TGF-β ligand expressed in these cells, leads to loss of GSCs). Increased gbb also leads to a more modest decrease in GSC proliferation rates during aging than in wild type. Further verifying the importance of the somatic niche cells immediately adjacent to the GSCs in aging, both groups show that E-cadherin, which contributes to the adherens junctions between GSCs and their niche, also declines during aging. Pan et al. additionally show that increasing E-cadherin expression either in niche cells or GSCs can lessen aging-related declines in stem cell number and function, presumably by strengthening the interactions between these cells.

These papers together thus demonstrate an integral role for the local microenvironment in promoting aging of GSCs. It seems clear, however, that other factors will also be involved in stem cell aging, as in both the ovary and testis, the extrinsic signals studied appear to only partially account for the changes observed. Intriguingly, Pan et al. show that overexpression of superoxide dismutase (SOD), which likely reduces oxidative damage to cells during aging, also leads to a decrease in aging-related phenotypes of GSCs. This is true not only when SOD is expressed in the somatic niche cells, but also when expressed solely in the GSCs themselves, strongly suggesting that GSCs might be aging intrinsically as well. Given this, it will be of great interest to know how these cells can overcome this damage to maintain the immortality of the germline as these cells contribute to future generations. In addition to cell intrinsic aging and aging of the local microenvironment, it is likely that systemic factors may also play a role in causing aging. Exploration of such issues will be of prime importance in evaluating the potential of stem-cell-based therapies to treat aging-related defects.

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